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Gabapentin (Neurontin®) improves pain scores of patients with critical limb ischaemia: An observational study

Gareth Morris-Stiff*, Michael H. Lewis

Department of Surgery, Royal Glamorgan Hospital, Ynysmaerdy, Llantrisant, Rhondda Cynon Taf, CF37 1JL, UK

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ABSTRACT

Objectives: The aim of this study was to assess the role of adding gabapentin (Neurontin®) to the prescription of patients with opiate resistant pain as a result of critical limb ischaemia (CLI).
Methods: An observational pilot study was performed on 20 consecutive patients with CLI who were taking all experiencing rest pain despite high dose opiate analgesia. None of the patients were candidates for reconstructive surgery or angioplasty due to the anatomical distribution of their vascular disease or presence of co-morbidities. Gabapentin was commenced at 300 mg daily and titrated to 300 mg tds over 3 days. Doses were then increased up to 600 mg tds as indicated. Pain was assessed by visual analogue scoring at baseline, 4, 7, 14 and 28 days. Improvements in night pain and need for opiates were also noted. The primary end point was pain score at 28 days or until surgical intervention/death if these points occurred sooner.
Results: Nineteen of 20 reported significant night pain, 15 had gangrene or ulceration. Seventeen of 20 patients completed the full observation period of 28 days. Two patients required an operation and 1 patient died of a myocardial infarct. The pain scores fell from a median of 9 (inter-quartile range [IQR]) (7–9) at baseline to 5 (3–6) at 28 days. Improvement in pain scores was observed in 15/17 patients. Of the 17 completing the study, 16 had experienced rest pain at the time of referral of which 15 had significant benefit with gabapentin.
Conclusions: The study has demonstrated that gabapentin is a useful adjuvant in the management of CLI and leads to significant reductions in pain scores and improves night pain for most patients.

1. Introduction

CLI is defined as chronic ischaemic rest pain, ulcers or gangrene attributable to objectively proven arterial occlusive disease.[1] The term CLI implies chronicity and is to be distinguished from acute limb ischaemia and should be confirmed by determination of an ankle systolic pressure ≤50 mm Hg, a toe pressure of <30–50 mm Hg or an ankle brachial pressure index (ABPI) of <0.5. It has been estimated that 20% of patients with intermittent claudication will deteriorate to a state of CLI giving a calculated prevalence for CLI of 1% in men aged over 55 years.[2]

Critical limb ischaemia (CLI) poses a number of difficult challenges to vascular surgeons as it is a limb-threatening condition associated with disabling and difficult to manage pain, and for those suitable for surgery – either reconstructive or amputation, there is a high prevalence of concomitant cardiovascular disease leading to significant morbidity and mortality.[3]

Management of CLI is directed at pain control and maintenance of limb integrity. A study by the Joint Vascular Research Group (JVRG) of 409 patients presenting with CLI noted that 60% were treated primarily by vascular reconstruction or angioplasty; 20% required primary amputation and 20% some other form of temporising treatment.[4] When the cohort was reviewed at 1 year: 25% had undergone amputation; 55% had both limbs intact; and 20% had died.

For those not suitable for angioplasty or reconstructive surgery, and for patients whose symptoms recur following primary treatment, the mainstay of treatment is either amputation or conservative management through provision of adequate analgesia. Amputation itself, despite being a relatively quick and simple procedure, is associated with a significant peri-operative mortality of 5–20% with a 2-year mortality of 25–30% and a 5-year mortality of 50–75%.[5] There is also considerable morbidity in particular phantom limb pain.

The prescription of analgesia in CLI had traditionally revolved around the use of opioid agents. Whilst the pathogenesis of CLI

* Corresponding author. 1 Golygfa'r Eglwys, Maesycoed, Pontypridd, Rhondda Cynon Taf, CF72 8XR, UK. Tel.: +44 1443 650625.
E-mail address: garethmorrisstiff@hotmail.com (G. Morris-Stiff).

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certainly involves complex interactions between the macro- and micro-circulations of the limb, the condition is not fully understood. It has been suggested that neuropathic pain may be an important element of CLI[6,7] and this is certainly the case that ischaemia is a recognised cause of neuropathic pain.[8] If this is the case, then other non-opioid agents may be of some clinical benefit and indeed avoid some of the troubling side-effects associated with opioids. One such drug is gabapentin (Neurontin®) which is licensed for the treatment of all neuropathic pain conditions and has certainly been demonstrated to be of benefit in terms of pain relief and quality of life in diabetic neuropathic pain.[9]

No studies have so far evaluated the role of gabapentin in patients with peripheral vascular disease and there is only a single case report documenting its use.[10] The aim of this study was to prospectively evaluate the clinical effects in terms of visual analogue pain scores in a pilot study of patients with CLI who were on high dose opioid analgesics and not candidates for reconstructive surgery or angioplasty.

2. Methods

Between April 2004 and April 2005, 20 consecutive patients with critical limb ischaemia were recruited to this observational pilot study. All patients were under the care of a single vascular surgeon and all had CLI due to infragenicular peripheral vascular disease that was not amenable to angioplasty or reconstructive surgery (due to anatomical site or patient co-morbidities). In each case CLI was confirmed by the presence of an ankle systolic pressure less than 50 mm Hg.

All patients were taking high dose opioid analgesic agents, of various types, at the time of recruitment which had failed to adequately relieve the pain. The majority of patients were taking a combination of sustained release and on demand preparations either morphine sulphate or oxycodone. None of the patients had previously been prescribed gabapentin.

Cardiovascular risk factors were noted including the presence of a history of: hypertension; hypercholesterolaemia; angina; myocardial infarction; transient ischaemic attack or cerebrovascular accident. Smoking habit was also noted. Patients with a history of diabetes were excluded.

Gabapentin was commenced at 300 mg daily and titrated to 300 mg tds over 3 days. Doses were then increased up to 600 mg tds as indicated. Pain was assessed by visual analogue scoring at baseline, 4, 7, 14 and 28 days. Patients were asked to mark their pain from 0 to 10 with 0 representing a pain free state and 10 being equivalent to the worst pain ever on a linear analogue score.[11] Treatment was carried out on an outpatient basis.

Improvements in night pain were noted as was any reduction in the prescribed dose of opioid analgesics. The primary end point was pain score at 28 days or until surgical intervention/death if these points occurred sooner.

The median pain scores at the varying time periods were compared to baseline levels using the Mann–Whitney *U* test with statistical significance assumed at the 5% level.

3. Results

The study population consisted of 11 males and 9 females with a mean age of 68 years (Standard error of mean [SEM] $\pm$ 2.4 years).

The presenting features and cardiovascular risk factor profiles are summarised in Table 1. Seventeen of 20 patients reported rest pain, 19 had evidence of ulceration or gangrene and all bar 1 experienced night pain leading to disturbed sleep patterns.

None of these patients had undergone any previous lower limb arterial surgery and presented with infragenicular disease.

Tab1e 1
Clinical features and cardiovascular risk factor profiles of patients prescribed gabapentin.

	Frequency *n* (%)
Clinical features	
Rest pain	17 (85%)
Night pain	19 (95%)
Ulceration	12 (60%)
Gangrene	7 (35%)
Cardiovascular risk factors	
Hypertension	18 (90%)
Hypercholesterolaemia	14 (70%)
Angina	11 (55%)
Myocardial infarct	8 (40%)
Transient ischaemic attack	5 (25%)
Cerebrovascular accident	2 (10%)
Smoking (current or ex-smoker)	18 (90%)

Seventeen patients completed the 28 day follow-up period and did not undergo any amputation during this time. One patient was admitted as an emergency due to the presence of gangrene then developed chest pain at 14 days following commencement of gabapentin. A myocardial infarct was confirmed but despite optimal medical management he died of his coronary event. Two other patients showed no improvement in pain control necessitating amputation at 17 and 21 days.

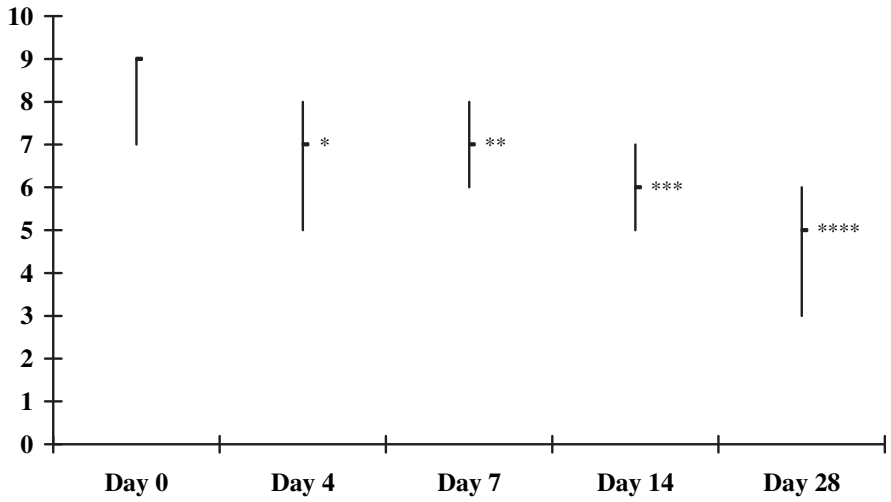
Of the 17 patients completing the study, the median dose of gabapentin was 1271 mg. Four patients were adequately controlled with 300 mg tds, 9 were on 1200 mg and the remainder were prescribed 600 mg tds. Of those taking 1200 mg of gabapentin, the additional drug dose was administered in the evening for night pain. None of the patients reported any specific undesirable side-effects related to gabapentin. In particular, daytime drowsiness did not appear to be a problem.

The median pain score for this cohort, as assessed by a visual analogue score, was 9 at presentation and was significantly reduced compared with the baseline at each of the assessment points and was 7 at 4 days; 7 at 7 days, 6 at 14 days and 5 at 28 days (Fig. 1.). Only 2 patients completing the follow-up period failed to show an improvement in pain scores. Of the 17 patients completing follow-up, sixteen had reported night pain at the time of recruitment of which 15 noted a significant reduction in night pain allowing better sleeping and a perceived improvement in the quality of life. In 5 patients, the improvement in pain control was significant enough to allow a reduction in the dose of opioid analgesics prescribed. None of the patients required increased doses of opiates.

4. Discussion

The primary finding of the study was that the addition of gabapentin to the standard opioid prescriptions of patients with CLI lead to a statistically significant reduction in median pain scores which was evident as soon as 4 days after commencing the new therapy. At recruitment the median pain score was 9 and this reduced sequentially over the course of the study to 5 at 28 days, a decrease of 44%. These results would suggest that the pain of CLI may include a component of neuropathic pain, possibly as a result of ischaemia to the sensory nerves.[6,7] In 5 cases the pain relief was successful enough to allow partial withdrawal of opioid medications thus reducing the prevalence of side-effects of these drugs which are extensive.

None of the patients reported any significant complications related to the gabapentin and none of the 3 who failed to complete the follow-up withdrew due to drug-related side-effects. Two of the 20 (10%) patients recruited ended up with an amputation and



*	p = 0.001	Day 0 vs. Day 4
**	p = 0.0002	Day 0 vs. Day 7
***	p = 0.0004	Day 0 vs. Day 14
****	p = 0.0003	Day 0 vs. Day 28

Data presented as median and inter-quartile range

Fig. 1. Median pain scores at baseline and at intervals of 4, 7, 14, and 28 days following commencement on gabapentin.

the third patient died as a result of cardiovascular disease. These findings are in keeping with those of the JVRG which indicated a significant proportion of patients with CLI will require amputation and a large number will die as a result of cardiovascular disease.[4] In contrast to Woolf's study, which reported the results of all-comers with CLI, this study concentrated on the worst prognosis group namely those patients not suitable for reconstruction due to unfavourable anatomy or cardiovascular co-morbidities. It also excluded diabetics, a group that is known to suffer from neuropathic pain and to benefit from gabapentin therapy.[9] Therefore, it is likely that if gabapentin were used in diabetic claudicants with CLI the results may be even more striking.

This is the first paper to investigate the role of gabapentin in a series of patients with CLI. The only existing literature is a case report published in 2005 of a 56 year old man with critical ischaemia who benefited significantly from gabapentin.[10]

In addition, of those reporting night pain, 15 of the 16 patients completing follow-up, reported a significant improvement in the severity of this symptom allowing them to obtain improved sleep. Whilst a formal quality of life assessment was not part of the design of this investigation, the majority of patients noted that improvement in the quality of their sleep was a great benefit to them.

The issue of night pain has for a long time been recognised as being of great importance in CLI as for many patients, this is one of the most crippling symptoms as it reduces their energy reserve for the following day.[12] Night pain occurs as a result of circadian changes in blood pressure control leading to nocturnal hypotension in an already ischaemic limb. It has been shown that the degree of hypotension correlates with the severity of night pain.[13] It may be that the improved control of night pain was related in part to one of the documented side-effects of gabapentin namely somnolence. However, as the majority of patients more than the baseline level of gabapentin took additional doses at night, this did not affect their level of daytime activity and drowsiness did not appear to be a significant problem.

The dose of gabapentin in this study was titrated to patient pain levels rather than a fixed drug level, and whilst significant improvement in pain scores and night pain were noted, it may have been the case that increasing doses to 600 mg tds for all patients would have lead to further improvements in symptomatic outcome. However, it is impossible to be certain that this would not have been associated with an increase in frequency of side-effects.

Further studies are planned to assess the role of intervention with gabapentin earlier in peripheral vascular disease by assessing its efficacy in patients with significant intermittent claudication prior to the development of CLI to determine whether pharmacotherapy in addition to risk factor modification and exercise programs can reduce the proportion of patients developing CLI. There is evidence that there is progressive neuro-degeneration which commences in intermittent claudication and progresses as the severity of the vascular disease progresses.[14] Formal quality of life studies will be included in these studies to confirm the findings of this observational study.

5. Conclusions

The study has demonstrated that the use of gabapentin as an analgesic in the management of CLI and leads to significant reductions in pain scores and also improves night pain for the majority of patients.

Conflict of interest
The authors declare no conflict of interest in relation to this paper.

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Ethical approval
The study was approved by the institutional research and development board.

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